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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,162	07/10/2003	Laszlo Vigh	CytRx/009 DIV2	4065

1473 7590 06/11/2008

ROPES & GRAY LLP
PATENT DOCKETING 39/361
1211 AVENUE OF THE AMERICAS
NEW YORK, NY 10036-8704

EXAMINER	
GEMBEH, SHIRLEY V	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
06/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,162	VIGH ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-22 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-22 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed **2/19/08** presents remarks and arguments to the office action mailed **10/16/07**. Applicant's request for reconsideration of the rejection of claims in the last office action has been considered.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of Claims

Claims 20-22 and 26-32 are rejected. Claims 1-19 and 23-25 have been cancelled and Applicant reserves the right to pursue the cancelled claims.

Specie Election, Applicant has asked that the specie election be pyridine instead of pyrimidine.

Maintained Claim Rejections - 35 USC § 112

Applicant argues that the examples on pages 112-134 of the instant application are enabled by asserting the US Patents 6,653,326 and 7,148,239. That, two different U.S. patent examiners have, at the very least, accepted the nexus between the disclosure and working examples of the instant specification and enablement of the claimed

therapeutic methods using compounds of the invention. Turning to the presently claimed subgenus, those of Formula r', the compound produced in Example 64 (p. 71, paragraph 220) (heretofore referred to by its colloquial name "iroxanadine") falls into the Formula I" subgenus of the pending claims and also corresponds to the presently elected species. Iroxanadine was subjected to the same heat stress experiments in the same working examples of the instant specification (see, e.g., Example 19 at pp. 124-133 of the specification) as were the compounds supporting enablement of the claims of the parent and sister applications that issued as the '326 and the '239 patents, respectively.

Applicant also argues that compound 13 of the patent '741 shows improvement of the endothelial function by decreasing vasodilation significantly. That encompassed by currently pending claim 20. As in Exhibit C describes the results at col. 3, line 55 -- col. 4, line 30 that provides support for methods of prevention as recited in the currently pending claims, because the effective compound was administered 6 hours *before* the physiological stress was induced in the white rabbit.

Also in application Us 2006/0058294 Applicant asserts that the oxadiazines of Examples 6-11 are shown in paragraphs 90-91 on pp. 3-4 to improve the functioning of the endothelium following a physiological stress (relating to endothelial function and vasorelaxing effects of compounds during chemically-induced vasodilation in thoracic aorta of spotanteously hypertensive ("SH") rats as described above for Exhibit C). Further evidence of the therapeutic effectiveness of these compounds is provided in the endothelial cell wounding migration assay set forth in paragraphs 86-88 on p. 3. The

oxadiazines referred to in Examples 6-11 are all encompassed by the (Formula I") genus of pending claim 20.

In response, each Application is examined on its merit. The claimed invention is that the compounds of claim 20 is used treating a disease connected with function of chaperone system or associated with the injury of the membrane of a cell organellum or preventing the same. As discussed in the last office action, these diseases are so diverse in nature that one cannot envision the treatment with the compounds of claim 30, let alone prevention of these numerous diseases.

For example viral disease, bacteria, tumor and immune disease alone is cumbersome. Immune disease can occur anywhere on the body and up to date there has been no one particular drug to treat every cancer, every immune disease every bacteria every allergenic disease for example as claimed.

As stated in the last office action, Applicant disclosed the mechanism(s) by which stress (physical, pathophysiological, etc.) is detected as a signal and transduced to the transcriptional apparatus is hitherto unknown. So if the mechanism of stress in unknown how than is it prevented?

Careful consideration is given but found not persuasive.

Claims 20-22 and 26-32 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

The Breadth of the Claims

The instant claims are directed to a method of treating a disease connected with the function of chaperon system or associated with the injury of the cell membrane of a cell or a cell organellum or preventing the same by administering to a host that is exposed to a physiological stress accompanying allergic diseases, immune diseases, autoimmune diseases, diseases of viral or bacterial origin, tumorous, skin and/or mucous diseases, epithelial disease of renal tubulus, atherosclerosis, coronarial disease, pulmonary hypertonia, cerebrovascular ischemia, stroke, or traumatic head injury an effective amount of a chemical compound to increase the expression of the molecular chaperon by the cell beyond the amount induced by the physiological stress,

wherein the chemical compound is one or more of a hydroxylamine derivative represented by formula (I").

The instant claims are also directed to treating (i) a disease connected to the function of chaperon, (ii) associated with the injury of the cell membrane and (iii) preventing the same in an eukaryotic cell that is exposed to a physiological stress comprising: treating the cell that is exposed to a physiological stress accompanying allergic diseases, immune diseases, autoimmune diseases, diseases of viral or bacterial origin, tumorous, skin and/or mucous diseases, epithelial disease of renal tubulus, atherosclerosis, coronarial disease, pulmonary hypertonia, cerebrovascular ischemia, stroke, or traumatic head injury with an effective amount of a chemical compound to increase the activity (see also bystress.com). These diseases are very broad an encompasses a very wide variation of diseases for example tumor (breast, lung pancreatic brain etc)

The Nature of the Invention.

The nature of the invention relates to using compound of formula I" for the treatment of a very wide variety of diseases that are associated or connected with the functions of chaperon, injury of the membrane or prevention. Several examples of are given in the specification on pages 112-134, for example, using different types of hydroxylamine compounds. However, the showing of the activity of these compounds does not provide a adequate support to enable one to practice the instant methods to treating (i) a disease connected to the function of chaperon, (ii) associated with the injury of the cell membrane and (iii) methods of preventing. See Applicants' own admission (see para

00353, pg 21 of the published application) using the specification as a dictionary. The mechanism(s) by which stress (physical, pathophysiological, etc.) is detected as a signal and transduced to the transcriptional apparatus is hitherto unknown. The prior art does not recognize treatment modalities for prevention of the recited conditions. See oncolink wherein non-Hodgkin's lymphoma (see underlined) is taught to be connected with a chaperon system. Identifying one pathway does not necessarily yield treatment for a wide variation of diseases. These diseases are very complex and usually have multiple etiologic factors involved.

Adequate guidance Applicant has not provided enablement for various aspects of the claimed methods. The skilled artisan in this field would not accept the representations set forth in the instant disclosure as sufficient to enable methods directed to treating (i) a disease connected to the function of chaperon, (ii) associated with the injury of the cell membrane and (iii) methods drawn to prevention. Further, Applicant has not demonstrated sufficient guidance in the form of adequate supporting representations or art recognized correlations in patent or non-patent literature. For example, Applicant only discloses examples on pages 80-85 to show how to make the formulations, and on pages 85-91, treatment of heat shock and or induction of heat stress cardiac ischemia. However, Applicant has not provided direction in the form of representative examples to show that the combinations of the functional groups claimed would have efficacy in the prevention of a wide variation of diseases as claimed.

The use of compound formula I" to treat or prevent a wide variety of stress conditions (see enclosed different types of physiological stress) is not possible absent

factual evidence. It is beyond the skill in the art to envision one drug that will treat all of these various stress forms, such as stroke, gastric problem, eating, pain, sleep disorder etc.

The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure

In order to provide support for the claimed methods comprising (i) treating a disease connected to the function of chaperon, (ii) treating a disease associated with the injury of the cell membrane and (iii) preventing with a hydroxylamine compound of formula I", it would be necessary to demonstrate (i) or (ii) how to extrapolate these data from in vitro to in vivo. The specification fails to provide support for the claimed subject matter. Therefore, one of skill in the art would require a significant amount of experimentation in order to find first which disease is associated with chaperon, associated with injury of the cell and further a means of prevention. No data from the disclosed examples indicate how the skilled artisan can go about preventing such stress which, according to Applicants own words is still unknown. In order to Practice the claimed invention, one skilled in the art would have to first envision an appropriate animal model and then set forth parameters drawn to prevention. Administration of the claimed compounds and test model system to determine whether or not a compound would follow in an appropriate is effective for prevention of said diseases. Although a showing of mimicking or treatment disease, this does not support a wide variety of diseases may be treated or prevented can be demonstrated.

The Existence of Working Examples

A lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught of using one drug for the prevention of so many diseases connected with function of a chaperon system.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

Nature of the Invention: Claim 21 is drawn to a method of treating/preventing, pathological conditions such as neoplastic disease, an infection caused by pathogenic microorganism, autoimmune disease and dermatosis with compound of formula I". The nature of the invention is extremely complex in that it encompasses the prevention of pathological conditions such as neoplastic disease (which itself encompasses a very wide variety of different types of pathology). As defined, neoplastic diseases are different diseases that start and evolve each in its own manner and trigger variable responses from the organism depending upon the pathologies of the neoplastic process. The clinical incidence of the different cancers is spread through the human life span, with regional differences for each cancer. (see CiteSeer abstract). With regards to dermatosis the term is encompasses skin cancer, eczema, psoriasis, acne, impetigo, scabies and warts. it is not clear how a single drug is capable of treating such a wide variety of diseases (see MSDS HyperGlossary enclosed).

The nature of the invention is very broad, and the relative skill of those in the art is generally that of a Ph.D. or M.D. with expertise in the field of proliferative diseases. Each particular neoplastic disease/infection caused by a pathogenic microorganism or all autoimmune disease has its own specific characteristics and etiology. The unpredictability observed with single agent therapy to treat a very wide range of disease is substantial. The broad recitation " neoplastic disease/infection caused by pathogenic microorganism or autoimmune disease or dermatosis" is inclusive of many conditions that presently have no established successful therapies.

It is clear the art to which the present invention relates is highly unpredictable.

Maintained Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **20-22 and 26-32** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **17-34** of U.S. Patent 7148239. Although the conflicting claims are not identical, they are not patentably distinct from each other. The reasons are as follows:

> Both sets of claims refer to treating a disease connected to the function of the chaperon system or associated with the injury of the membrane of a cell administering to the host that has been exposed to a physiological stress a compound of formula **I**" –in the current application (claims 20-22) and formula II in the patented claims (**claims 17-33**).

As to the patented claims 17-34, these claims refer to a method of treating and a pharmaceutical composition. The pharmaceutical composition (see claim 34) would have been used in the claimed method of treatment because the compounds of formula I" (see specification taken as a dictionary, col. 86, lines 7-27) and the resulting compound of formula II would have been used in the treatment procedure. The

compound of formula I" is a derivative of compound of formula II. In view of the foregoing, the patent claims and the current application claims are obvious variations.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

SVG
6/6/08